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GROWTH AND GROWTH DISORDERS

CURRENT AND POTENTIAL THERAPEUTIC USES OF GROWTH HORMONE AND INSULIN-LIKE GROWTH FACTOR I

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THE THERAPEUTIC USE OF GROWTH HORMONE

Almost 4 decades have passed since the treatment of growth hormone deficiency with human pituitary growth hormone (GH) was first reported in 1958. [] Initially, the number of children treated with GH was small, and fewer than 100 patients were started on treatment in the United States in the following 4 years. The National Pituitary Agency was begun under the sponsorship of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) in 1962 to organize the collection of pituitary glands at the time of autopsy and the purification and distribution of GH. The increase in the therapeutic use of GH in the United States was almost logarithmic for the next 2 decades, [] and by 1985 approximately 3000 patients in the United States were under treatment with human pituitary growth hormone (Fig. 1) (Figure Not Available) . Because of the limited supply of pituitary GH, only about half of the severely growth hormone deficient patients could be treated, doses of GH were limited and the supply of GH for the patients was often interrupted. In 1985, several patients who had been treated with pituitary GH were reported to have developed Jakob-Creutzfeldt disease at an unusually young age. [] Because of the potential risk of Jakob-Creutzfeldt infection, the use of pituitary growth hormone in the United States was stopped in early 1985. Fortunately, clinical trials of biosynthetic GH had been conducted since 1982, [] and several months after the withdrawal of pituitary GH the use of synthetic human growth hormone for the treatment of GH insufficiency was approved by the FDA in the United States. By the end of 1986 the number of patients on growth hormone in the United States had doubled to

Figure 1. (Figure Not Available) The estimated use of GH in the United States. The data represent the number of patients estimated to be on active treatment with GH in the United States from 1964 to the present and derived from National Hormone and Pituitary Program and commercial sources. The estimated number of patients on active treatment is plotted on a logarithmic scale *(From Hintz RL: Untoward events in patients treated with GH in the USA. Horm Res 38(suppl 1):44-49, 1992; with permission from Karger, Basel.)*

more than 6000, and there has been a steady increase in the use of growth hormone since that time. At present, more than 30,000 patients are actively on treatment with growth hormone, and since 1960 more than 50,000 children in the United States have been treated with growth hormone of either pituitary or synthetic origin (Fig. 1) (Figure Not Available) . The overall safety record of recombinant human GH has been good, although unfavorable clinical events associated with GH therapy have been seen. [] [] The majority of GH therapeutic use during the past 40 years has been to stimulate the growth of patients with classically defined GH deficiency; however, GH is a potent anabolic hormone with a wide variety of biologic actions, and there are many potential therapeutic uses for GH as either a growth promoting or metabolically active agent that are under active investigation. Because of the breadth and rapidly changing nature of this field, it is not possible to include all potential uses of GH in this article.

GROWTH-RELATED USES OF GROWTH HORMONE OTHER THAN GROWTH HORMONE DEFICIENCY

Chronic Renal Failure

Growth hormone has also been used for the alleviation of the severe growth failure associated with renal failure. [] Although a survey of the worldwide data

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supports the use of GH for this indication as a stimulator of growth rates, the studies do not permit the assessment of the impact of GH on adult height in these patients. In 1993, the FDA approved the use of GH for the treatment of growth failure caused by chronic renal disease before transplantation. It is important to emphasize that these patients must have careful management of the other medical problems associated with renal failure or they will fail to respond to GH. [] Recent studies have suggested that GH therapy is useful in patients with renal failure even while they are being treated with chronic dialysis. [] There has been some concern that patients may have an increased rate of progression of their underlying renal failure while on GH treatment, or that GH may increase the rate of rejection of renal transplants. [] The evidence is good that GH does not lead to the progression of renal failure, [] but whether the rate of rejection of transplants is increased is a topic of active study and must be regarded as unsettled.

Turner Syndrome

Of the nontraditional indications for GH therapy, the one that seems to have the best support by data is its use for promotion of growth rate and final height in Turner syndrome. Short stature is an almost universal feature of patients with Turner syndrome, and it is a significant part of the long-term problems that these patients face as adults. Attempts to treat the short stature of patients with Turner syndrome with androgens or estrogens have been of marginal usefulness at best. [] Most women with gonadal dysgenesis have an average adult height between 135 cm and 142 cm. Androgens can cause a short-term increase in the rate of growth of girls with the disorder but do not result in an increase in final adult stature. The use of GH for patients with Turner syndrome at doses within the range used for GH deficiency is associated with clear increases in the rate of growth. The Genentech Collaborative Group study of the effects of GH treatment on Turner syndrome that was started in 1983 has demonstrated that the use of GH with or without additional androgens led to a significant increase in both growth rate and projected adult height. [] The long-term results of this study have shown the usefulness of GH therapy on increasing the final height of patients with Turner syndrome. [] The results of this collaborative US study have been confirmed by other trials of GH therapy from around the world. [] [] [] GH-treated patients with Turner syndrome seem to achieve an increase in final height averaging more than 8 cm when compared with their predicted height potential (Fig. 2) (Figure Not Available) . This data is confirmed by the large experience with GH treatment of Turner syndrome from the National Collaborative Growth Study (NCGS) in the United States. [] The 230 naive Turner patients in the NCGS study who had a mean duration of GH treatment of 4.3 years are calculated to have an overall mean increase in their final height over their initial projected height of 8.9 cm. Although the use of GH for Turner syndrome has been approved by many countries, it has not yet been approved as an indication for GH therapy by the FDA.

Non-Growth Hormone Deficient Short Stature

The potential usefulness of GH as a growth stimulating therapy for patients with significant growth retardation who do not fulfill the "classic" diagnostic

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Figure 2. (Figure Not Available) Turner growth in response to GH and oxandrolone treatment. Normal female growth percentiles from the National Center for Health Statistics *(dotted lines)* and Turner syndrome growth curves *(solid lines). A,* Recipients of **hGH** alone, before treatment. *B,* Recipients of **hGH** alone, during or after treatment. *C,* Recipients of combination therapy, before treatment. *D,* Recipients of combinations therapy, during or after treatment. , Before treatment or after cessation of therapy; , during treatment. *(From Rosenfeld RG, et al: Six-year results of a randomized, prospective trial of human growth hormone and oxandrolone in Turner's syndrome. J Pediatr 121:49-55, 1992; with permission.)*

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criteria for GH deficiency is under investigation. Most children with significant short stature have a peak GH level in response to provocative testing above 10 ng/mL and therefore do not have GH deficiency by that standard; however, it is clear that many of these children without classic GH deficiency respond to GH treatment with at least an initial increase in growth rates and predicted adult height (PAH) (Fig. 3) (Figure Not Available) . Many of these patients have low levels of insulin-like growth factor (IGF)-I, IGF binding protein (IGFBP)-3, or GHBP and may have a subtle defect in the GH-IGF axis, but some are not distinguishable from the normal range by any available laboratory test. Several multicenter trials of GH therapy in these patients are underway, and they show increases in the height standard deviation scores and predicted adult heights in many of these patients. [] Whether the final height of these children after GH treatment is greater than their predicted height is not established, however. Some studies on the long-term results of GH treatment of significantly short children treated with GH who do not have classic GH deficiency suggests that there is an increase in mean final height with GH therapy. [] [] Other authors do not agree with this conclusion [] [] , however. Even in those studies that report a significant effect of GH therapy on PAH, a large proportion of patients do not achieve clinically significant benefit, as judged by an increase in height of at least 5 cm.

Figure 3. (Figure Not Available) Growth rate response with GH treatment of patients with compared idiopathic short stature (ISS) with untreated controls. , recipients of GH therapy; , untreated controls. *(From Hopwood NJ, et al: Growth response of non-growth hormone deficient children with marked short stature during three years of growth hormone therapy. J Pediatr 123:215-222, 1993; with permission.)*

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Only the completion of studies to adult height will provide a firm basis for recommendations about treatment in this group of patients. It is hoped that the results of trials to final height may give some indication of which category of idiopathic short stature (ISS) patients are most likely to achieve benefit from GH therapy. In the meantime, the debate about the ethical and practical considerations associated with the widespread use of GH treatment for this type of patient will continue. []

Other Proposed Uses of Growth Hormone in Patients with Short Stature

Growth hormone has also been used to treat small numbers of subjects with a wide variety of other growth disorders associated with short stature, including skeletal dysplasia; [] spinal bifida; [] and other genetic syndromes, such as rickets, [] Prader-Willi syndrome, [] and Down syndrome. [] In many of these potential uses, GH has been demonstrated to produce short-term increases in growth rates; however, in none of these conditions are there enough long-term data to be certain that GH therapy produces an increase in final adult height. There also have been studies of using the combination of GH and gonadotropin-releasing hormone (GnRH) to increase final adult height. [] Whether this interesting approach is useful [] must await the results of other studies in progress.

METABOLIC USES OF GROWTH HORMONE

The therapeutic use of GH is not limited to its growth promoting properties. The administration of GH to normal subjects results in prompt and reproducible effects on metabolism, including nitrogen retention, an increase in insulin resistance, and an increase in total energy expenditure. [] Thus, there has been interest in the use of GH as an anabolic agent.

Adult Growth Hormone Deficiency

It has been the impression of many endocrinologists that adult patients with GH deficiency are weak, have poor energy levels, and have a diminished overall feeling of good health. These patients often complain of lethargy and fatigue despite adequate thyroid, adrenal, and gonadal hormone replacement therapy. [] Rosen and Bengtsson [] have reported on 333 patients with panhypopituitarism and GH deficiency who had routine standard hormone replacement therapy without GH treatment as adults. [] This group of patients had a cardiovascular death rate nearly twice that of the general population. The authors speculated that this increased mortality was a result of GH deficiency and the accompanying hypercholesterolemia. Several controlled studies of GH therapy in GH-deficient adults have been published. One double-blind, placebo-controlled crossover study of the effects of GH therapy in young GH-deficient adults revealed an increase in thigh muscle volume; a decrease in adipose tissue volume; an increased exercise capacity, renal blood flow, and glomerular filtration rate; and an enhanced sense of well-being with GH treatment. [] These studies are very promising, and controlled long-term intervention trials on the

GH treatment of adult GH deficiency are underway. The use of GH therapy for adults with GH deficiency has been approved in several countries but not yet in the United States.

Lipid and Carbohydrate Metabolism

Because of the known effects of GH on **lipolysis** and body composition, several studies have investigated whether GH would be useful as a treatment for obesity. [] So far, the studies have not shown any long-term benefit of GH in the treatment of obesity, although short term increases in lean body mass and decreases in fat mass have been shown. Whether GH, in combination with other therapeutic strategies, is useful in the long-term treatment of obesity is a subject of ongoing investigation. Other studies have shown that GH therapy modulates the levels of lipids in the circulation. [] It has been proposed that GH may have a beneficial effect on the atherogenic risk of patients with GH deficiency. []

GH treatment also has been shown to be useful in the treatment of non-islet cell tumor hypoglycemia. [] The hypoglycemia in these rare cases seems to be caused by both an increase in the amount of IGF-II prohormone, and a disturbance of the macromolecular distribution of the IGFs in the circulation. GH therapy leads to a decrease in the small molecular weight IGFs that cause the hypoglycemia. Another unusual proposed use of GH is for the treatment of patients with methylmalonic aciduria. []

Fertility

It is now known that the GH-IGF axis has a major influence on the functioning of the ovaries and testes. [] Local production of IGF seems to be an important component in gonadal cellular function, and it is under the dual control of GH and gonadotropins. Because of this, some investigators have suggested that GH might be useful in the treatment of infertility, and several studies have been performed in this area. Although early reports of GH use in infertility were encouraging, recent studies have been less positive. [] The use of GH for these indications must be regarded as still speculative.

AIDS

The use of GH therapy in acquired immunodeficiency syndrome (AIDS) is being explored both for the anabolic effects of GH and for its potential effects on the immune system. [] One of the major problems in the management of AIDS is the severe wasting of body tissues that frequently develops. This severe catabolic state contributes to the risk of infections, and the patients inability to respond effectively. GH is a potent anabolic agent, and GH therapy has been investigated to determine if it can alleviate or reverse the malignant catabolic state that develops in AIDS. One short-term study [] on the use of GH in AIDS wasting gave encouraging results, and longer term studies are now in progress.

Elderly

Because of the relatively low levels of GH and IGF-I in aging adults, it has been hypothesized that many people beyond the sixth decade of life are functionally

GH deficient and might benefit from GH therapy. [] Several investigators have conducted controlled studies using GH therapy in aging adults. [] Definite changes have been seen in nitrogen retention, body composition, [] bone turnover, [] and perhaps bone density; however, it seems unlikely that GH therapy will be the universal rejuvenative agent for all the ills of aging. GH therapy may be useful in elderly patients as part of a multifaceted therapeutic approach involving exercise or other therapeutic interventions; however, the therapeutic ratio of GH therapy in the aging adult seems to be rather narrow.

Other Uses of Growth Hormone as an Anabolic Agent

In many clinical situations, the catabolic state is a major barrier to the recovery of the **patient**. It was logical to study GH, with its potent anabolic actions, as a therapeutic agent in these disorders, and many of the clinical situations associated with a severe catabolic state have been explored in at least a preliminary way. These studies include **wounds**, [] burns, post-trauma or surgery cachexia, [] dialyzed patients with renal failure, [] sepsis, [] and cancer cachexia. [] One of the best studies of these clinical problems is burns. Patients with burns are severely catabolic, which limits their ability to synthesize new tissues. Studies by **Herndon** and co-workers [] [] have shown that GH treatment promotes donor-site healing in severely **burned** children and adults. The effects of GH on carbohydrate metabolism in these patients may limit the doses of GH that can be safely used, however. Postoperative patients are also severely catabolic, and GH treatment is actively being studied for this indication. Patients treated with total parenteral nutrition (TPN) may continue to be catabolic despite the delivery of what is calculated to be adequate calories and other nutrients. Studies have shown that GH therapy in combination with TPN moderates the overall catabolic state and particularly improves the protein-sparing effect. [] Active investigation of the use of GH therapy as an anabolic agent and an important adjunct to disease specific treatment is ongoing in several other clinical situations, including cancer cachexia and amyotrophic lateral sclerosis.

At this point, none of these situations can be regarded as an established indication for GH treatment. GH has been shown to be a potent metabolic agent in most of these clinical states; however, in many of these catabolic illnesses, the therapeutic ratio of GH treatment is marginal, frequently because of the insulin-resistance effects of GH. Because the carbohydrate metabolism of many of these patients is already stressed, the addition of GH treatment in many of these patients has led to carbohydrate intolerance. This has limited the dosage of GH that can be safely used in catabolic illnesses, and has led to the exploration of the direct use of the mediator of GH anabolic action, IGF-I.

POTENTIAL THERAPEUTIC USES OF INSULIN-LIKE GROWTH FACTOR I

Growth Related Uses of Insulin-like Growth Factor I

The clinical applications of IGF-I have been under active investigation. [] [] Since the classic description by Laron [] of the syndrome that is now frequently referred to as *GH insensitivity syndrome* (GHIS), it was realized that these patients are severely resistant to the biologic effects of GH. It is now clear that these

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patients have one of a variety of genetic defects in the *GH receptor* gene. [] The somatomedin hypothesis would predict that, because somatomedin (IGF) is the mediator of the growth effects of GH, patients with GHIS would grow in response to IGF-I therapy. There are now a number of studies from around the world [] [] [] [] that have demonstrated that GHIS patients grow with IGF-I therapy (Fig. 4) (Figure Not Available) , thus providing validation of the somatomedin hypothesis in an in vivo model. IGF-I has also been useful in the treatment of acquired resistance to GH caused by antibody formation in patients with complete GH deficiency caused by defects in the GH gene. Although the number of patients with these severe forms of GH resistance is very small, some patients with partial GH resistance may benefit from IGF-I treatment. Recent work has identified patients with heterozygous defects in the GH receptor gene within a selected population of children with short stature who did not have classic GH deficiency. [] Further studies are needed to determine the prevalence and biologic relevance of this finding in a less selected group of patients with short stature and whether GH or IGF-I would be the most effective treatment.

Figure 4. (Figure Not Available) Growth rate of a child with GH insensitivity syndrome treated with twice-daily subcutaneous injections of IGF-I (120 mug/kg per dose). Height was measured at 1- to 4-week intervals (). Also shown are predicted increases in height during the same period based on pretreatment height velocity (6.5 cm/yr) and 50th percentile growth curve for normal boys of the same age. Inset: **Patient's** annualized height velocities calculated during 0.8 year before treatment () and during treatment with IGF-I (). These are compared with 50th-percentile height velocities (± SD) for boys of the same chronological age (CA; *hatched bar*) and bone age (BA; *back-hatched bar*). *(From Walker JL, Van Wyk JJ, Underwood LE: Stimulation of statural growth by recombinant insulin-like growth factor I in a child with growth hormone insensitivity syndrome [Laron type]. J Pediatr 121:641-646, 1992; with permission.)*

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Potential Uses of Insulin-like growth factor I as an Anabolic Agent

Many of the growth-promoting and anabolic biologic activities of GH are caused by its indirect actions through the IGFs rather than direct actions of GH. Because IGF-I is insulin-like and does not lead to insulin resistance, there is reason to believe that in some instances it may be a better-tolerated and more effective therapy for catabolic illness than GH. In addition, its inherent insulin-like biologic actions might be useful in the treatment for **diabetes.**

Diabetes Mellitus

The use of IGF-I therapy to improve the control of adult-onset (type II) **diabetes** has been investigated. [] [] So far, the number of side-effects associated with IGF-I treatment has outweighed the benefits; however, some investigators think that a lower dose of

IGF-I might produce a useful metabolic effect without leading to side effects. Studies using a variety of therapeutic regimens are now in progress. The use of IGF-I to treat insulin-resistant **diabetes** caused by a mutation in the insulin receptor also has been reported. [] Preliminary data [] [] suggest that IGF-I might be useful in establishing better control of juvenile onset (type I) **diabetes**. Longer term studies of the use of IGF-I in type I **diabetes** are being conducted. In addition, the use of IGF-I in patients with severe insulin resistance and **diabetes**has been reported in insulin-resistant type A patients, [] and in leprechaunism. [] IGF-I therapy in these rare syndromes has been useful in some patients but not in others.

Other Proposed Uses

Almost any catabolic disorder in which GH therapy may be useful would in theory also respond to IGF-I treatment. This would include adult growth hormone deficiency (GHD); [] AIDS, elderly patients; [] and other catabolic illnesses, such as trauma, burns, [] and postsurgery catabolism. Because the changes induced in carbohydrate metabolism seem to limit the practical usefulness of GH therapy in some of these situations, the use of IGF-I has theoretic advantages because it does not cause insulin resistance. So far, the limited information available on the use of IGF-I treatment for catabolic states is promising but not conclusive. Herndon and co-workers [] [] have shown that IGF-I therapy after burn injury reduces gut atrophy [] and improves hepatic energy metabolism. It has also been suggested that IGF-I might be useful in the treatment of tumor cachexia, myotonic dystrophy, [] lipid disorders, Werner syndrome, [] and Rabson-Mendenhall syndrome. [] Further exploration of the use of recombinant IGF-I in catabolic states is being actively pursued in several centers [] but is not yet published.

The research on the therapeutic uses of IGF-I is far behind research on the uses of GH. So far, only the use of IGF-I to stimulate growth in patients with severe GHIS can be regarded as established, and even this use has not been approved by the FDA. The rest of the proposed therapeutic uses of IGF-I are fascinating but unproven.

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TABLE 1 -- THERAPEUTIC USES OF GH AND IGF-I

Approved therapeutic uses of GH in the United States

Poor growth in patients with GH deficiency and insufficiency

Poor growth caused by chronic renal failure

Probable uses of GH

Turner syndrome

Adult GH deficiency

Potential uses of GH

Non-GH deficient short stature

Catabolic illnesses

Approved therapeutic use of IGF-I

None

Probable use of IGF-I

GH insensitivity syndromes

Potential uses of IGF-I

Diabetic mellitus

Catabolic illnesses

SUMMARY

The accepted and potential uses of GH and IGF-I are summarized in . In general, the research on the therapeutic uses of IGF-I is at a much earlier state of development compared with GH. The use of GH in the treatment of children with GH deficiency is well accepted, and its use in the treatment of short stature of renal failure also is widely accepted. The FDA has approved the use of GH in children with short stature caused by GH insufficiency and renal failure. The use of GH in patients with Turner syndrome has not been approved by the FDA, although it has been approved in several other countries. The use of GH for the treatment of adults with GH deficiency is approved in several countries but it is not approved in the United States. With the exception of the cases with GHIS, the use of IGF-I as a therapeutic agent cannot yet be regarded as of proven usefulness. The potential uses of GH and IGF-I are an area of active investigation and will continue to enlighten our understanding of human disease and disorders of growth.

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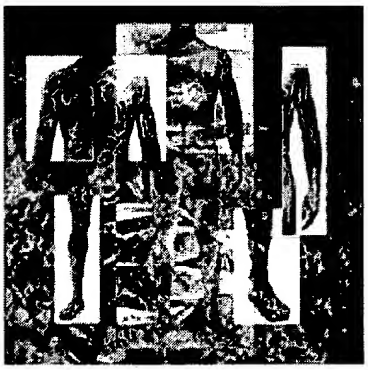
THIS WEEK'S LEAD STORY

THE ULTIMATE INJURY

Cytokines mark the new frontier for treating major burns



NEW YORK-Betty Shabazz's burns made her whole body weep.

The fire that destroyed 90% of her skin set off microvascular leaks that affected every organ and led to extreme edema. At the same time, histamine, bradykinins, and oxygen free radicals released by burns increased vascular permeability.

In the kind of burn that the widow of Malcolm X suffered, all body processes accelerate. Metabolism, core temperature, protein breakdown, lipolysis, and stress hormones increase. Patients lose muscle and become more susceptible to infection. Pain activates the limbic system.

Because of massive edema, patients are hugely swollen, occasionally doubling their original weight. But if they aren't adequately nourished their muscle mass can waste away. "You're as sick as you can get," says Dr. David Heimbach of the University of Washington's burn center.

While better nutrition, early debridement, improved grafts, and artificial skin have boosted survival rates, new layers of complexity in burn wounds are emerging, according to interviews and to reports at the American Burn Association meeting here. Cytokines, especially interleukins 1 and 6 and tumor necrosis factor, may be key to many of the local and systemic effects. They're called the new frontier of burn

therapy.

IL-1 receptor antagonist has been tried as adjunctive therapy for postburn sepsis. But its efficacy is dose-dependent in a narrow window, and it may require individual dosing based on IL-1 levels, says a Cincinnati Shriners Burns Institute report.

Researchers there think that IL-1 and tumor necrosis factor promote muscle catabolism after burn injury by blocking the anabolic effect of insulin-like growth factor. But their studies indicate that IL-1 and TNF don't induce muscle proteolysis by a direct effect or by inhibiting IGF-1.

IL-4 and IL-6, which down-regulate the inflammatory response, were studied in 14 burn patients by Dr. John Cone's University of Arkansas team. Serum levels of IL-4 and IL-6 weren't markedly elevated after serious burns, but IL-4 levels were much higher in the nine who survived.

Fluid resuscitation is the first step in therapy. Patients may get 20 to 30 liters the first day and need almost as much the second, says Dr. Bruce Greenstein, head of the Jacobi Hospital unit here that treated Shabazz. Some compare it to filling a sieve. At Cincinnati Shriners, a duodenal tube is inserted on admission for enteral feeding, based on the burn size, patient's age, and status. Dr. Michele Gottschlich says the tube-feeding menu-25% protein, folic acid, vitamins A and C, multivitamins, and zinc-almost doubles the patient's preburn caloric intake.

Dr. Gottschlich says if food does not get into the gut, its microvilli atrophy and GI infections are more likely. But despite careful nutrition, burned children lose lean body mass, becoming peripherally skinny and centrally fat. Growth hormone can reduce their weight loss and stimulate protein synthesis, says Dr. David Herndon's team at the Galveston Shriners Burns Institute.

Cerebral symptoms in burns are more prevalent than realized, says Dr. Hugo Linares, a Galveston Shriners pathology researcher. He says about 90% of autopsies of burn patients' brains showed generalized edema and focal or diffuse neuron loss.

Heart output falls precipitously after a burn, and cardiovascular function mediators such as epinephrine, norepinephrine, vasopressin, and angiotensin II increase. Even moderate thermal injury can cause myocardial dysfunction, and Dr. Joseph Murphy of UT Southwestern in Dallas suggests

using troponin I as a more specific marker than CPK or its MB isoenzyme. In a study of 21 patients he found troponin I increased a mean 4.5 hours after injury.

To decrease cardiac work, prolonged use of propranolol is safe, says Dr. Herndon's team. It found the average heart rate fell 10% to 13% in 23 youngsters who were given 0.5 to 1.0 mg/kg of oral or IV propranolol every eight hours for 10 days.

Hematopoiesis is changed by burns. Platelets and red and white cells fall, and bacterial proliferation in the eschar attracts neutrophils that release large amounts of proteolytic enzymes and inflammatory mediators.

Thromboembolic complications may be underestimated. A U.S. Army team at Fort Sam Houston found 1.77% of 1,300 burn patients had DVT or pulmonary embolism. The sum of a patient's age and area burned can show the risk, it says.

The liver may increase to twice its normal size and cause breathing problems by restricting the diaphragm.

Acute renal failure is relatively rare in burn patients but often fatal. Most frequently the result of fulminant sepsis or multiple system organ failure, it may respond to continuous veno-venous hemodialysis, says Dr. Donald Parks' Houston team. But 5% of 406 patients developed renal failure at Detroit Receiving Hospital's burn center, Dr. Jai Prasad's team reported, particularly those dehydrated from drinking alcohol.

Osteoporosis, new bone formation, and pericapsular calcification are fairly common after burns because of immobilization, hyperemia, and adrenocortical hyperactivity, says Dr. E. Burke Evans of the Galveston Shriners.

Cornell physiotherapist Robin Silverberg says heterotopic bone forms most often around the elbow, and she has treated many burn patients for frozen shoulders, joint capsular tightness, and peripheral neuropathy. She finds rehabilitative therapy more complicated after burns than after spinal-cord injuries. *-Elsie Rosner*

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